

Systematic review of immunotherapy for chronic rhinosinusitis

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ABSTRACT

Background: Immunotherapy (IT) has been well established as an effective treatment for allergic rhinitis (AR), but little is known about the benefits of IT on clinical outcomes of comorbid chronic rhinosinusitis (CRS). The goal of this publication is to systematically review the literature regarding outcomes of IT in patients with atopic CRS.

Methods: A systematic review of the literature was conducted including studies that assessed the efficacy of IT on clinical outcome measures in CRS including without polyp, with polyp, and allergic fungal rhinosinusitis subgroups. Excluded articles were those only reporting outcomes specific to asthma or AR.

Results: Seven studies met the inclusion and exclusion criteria for this review, none of which were randomized controlled trials. Generally, symptom scores improved in patients treated with IT when compared with baseline data and control patients. Objective endoscopic exam measures improved with IT treatment in short-term studies. Significant improvements were observed in radiographic assessments, and there was a decreased necessity for revision surgery, interventional office visits, and intranasal and oral steroid use.

Conclusion: Conclusions are limited by the paucity of available data on the efficacy of IT for treating CRS-specific outcome measures. There is weak evidence to support the use of IT as an adjunctive treatment in CRS patients, particularly in the postoperative period.

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An estimated 20–60% of patients with chronic rhinosinusitis (CRS) have comorbid allergic rhinitis (AR).¹ It has been postulated that CRS and AR are manifestations of a similar disease process found in adjacent airway locations.² However, the impact of AR on CRS development and disease severity remains controversial. Repetitive exposure to offending antigens in AR results in increased eosinophil recruitment and migration as well as abnormal cytokine profiles leading to T-helper 2 cell skewing and chronic nasal inflammation.^{3,4} This nasal inflammation could predispose to CRS and/or exacerbate sinonasal symptoms by obstructing sinus ostia, leading to worse sinus-specific quality of life.⁵ Given these potential interactions, treatment of AR might be expected to improve CRS outcomes.⁶

Immunotherapy (IT) has been well established as an effective treatment for AR, inducing up-regulation of regulatory T cells and antigen-specific IgG, while decreasing antigen-specific IgE.⁷ Together, this dampens the immune response to offending antigens and decreases nasal inflammation. Several recent systematic reviews with meta-analysis document overwhelming evidence that subcutaneous and sublingual IT result in improved symptom scores and quality-of-life measures, as well as reduced need for pharmacotherapy in patients with AR.^{8–10} However, the majority of these studies excluded patients with CRS, and it remains unclear whether IT benefits will be seen in patients with comorbid sinus disease. The distinction between improvements in CRS and AR is also difficult given the level of overlap in symptoms and currently available assessment tools that generally combine elements of both disease states.

A limited number of studies have examined the efficacy of IT in atopic patients with CRS, both CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) as well as in subgroups with allergic fungal rhinosinusitis (AFRS). The goal of this study was to

systematically review studies in which IT was used and sinusitis-specific outcomes were measured in atopic patients with CRS.

METHODS

Search Method

This study was considered exempt by the Medical University of South Carolina Institutional Review Board. K. DeYoung and J.L. Wentzel contributed equally to this work. Two reviewers (K.D. and J.L.W.) independently performed literature searches in PubMed (1950 to June 2013) and Medline (January 1966 to June 2013) for studies investigating the effectiveness of IT in patients with CRS, including CRSsNP, CRSwNP, and AFRS subgroups. The keywords and Medical Subject Headings included “Immunotherapy” OR “SCIT” (subcutaneous IT) OR “SLIT” (sublingual IT) OR “immune tolerance” AND “sinusitis” OR “rhinosinusitis” OR “nasal polyps” OR “Samter’s triad” OR “aspirin-exacerbated respiratory disease.” “Humans” was the only limit used, and studies in all languages were reviewed. Additional articles were identified through review of the reference lists of all identified studies.

Inclusion/Exclusion Criteria

Studies that assessed the effect of IT on the symptoms, objective clinical measures, recurrence, or additional treatments in atopic patients with CRS were included. Studies assessing only conjunctivitis or asthma-specific symptoms were excluded. Data from identified studies were independently reviewed and extracted by three authors (K.D., J.L.W., and Z.M.S.).

Statistical Analysis

The primary outcome of interest was sinonasal symptom scores. Secondary outcome measures included endoscopic evaluations, polyp recurrence, revision surgery, radiographic assessment, medication requirements, and average number of office visits for sinusitis management. Data analysis included studies comparing IT as an adjunct to traditional medical therapies versus medical therapies alone in atopic patients. For controlled studies, an attempt was made to pool data *via* formal meta-analysis to generate the standardized mean difference between baseline and follow-up time points using a

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random effects model, given expected heterogeneity across studies. For outcomes in which meta-analysis was not possible, study data were reviewed individually with regard to each outcome of interest.

RESULTS

Search Results

The literature search resulted in 289 publications of which 7 met the inclusion criteria for analysis (Table 1). Figure 1 shows the literature search strategy in accordance with PRISMA guidelines.¹¹ There were no randomized controlled trials (RCTs) identified. Three publications are prospective non-RCTs,^{12–14} two are cross-sectional studies of the same prospective protocol,^{15,16} one is a retrospective case series,¹⁷ and one is a retrospective chart review.¹⁸ The articles, published between 1983 and 2004, describe a total of 353 atopic patients with CRSsNP, CRSwNP, or AFRS. Five of seven studies were limited to postoperative patients^{13–16,18}; one described children who had not been treated surgically,¹² and the last simply screened for 12 consecutive months of IT use regardless of surgical status.¹⁷ All studies confirmed atopic status using skin-prick testing or radioallergen sorbent test methods except one that identified atopy by a medical record diagnosis of AR.¹⁷ In all studies, IT was offered to patients as an adjunct to standard medical management strategies as outlined in Table 1. The type of IT used was either identified as subcutaneous^{12,15,16} or not specified.^{13,14,17,18} No studies specifically evaluated sublingual IT. The follow-up periods ranged from 3 weeks to 138 months, with a weighted mean follow-up of 34.3 months.

Symptom Scores

Two studies recorded symptom scores before and after treatment with IT and compared the data to atopic CRS patients who chose not to undergo IT.^{12,14} Asakura *et al.* found that the children receiving subcutaneous IT had significant improvements in sneezing, rhinorrhea, and nasal obstruction after 2–3 months of treatment ($p < 0.01$), whereas the otherwise medically managed atopic control group only improved in sneezing ($p < 0.05$) as scored by a standardized nasal symptom notebook. When the groups were compared at the conclusion of the study, the IT subset had significantly better scores in rhinorrhea and nasal obstruction symptoms than the atopic controls ($p < 0.01$). However, at baseline the sneezing score was significantly more severe in the IT group ($p < 0.05$), and the nasal obstruction score was more severe in the atopic controls ($p < 0.01$). A change from baseline comparison was not made between groups. Schlenter *et al.* came to similar conclusions by comparing an unspecified, semiquantitative symptom score measurement (higher scores indicate less severe symptoms) in atopic CRS patients using IT to a control group of atopic medically managed CRS patients at two follow-up points (4 months and several years). At 4 months, the IT group had less severe symptoms than the atopic controls (symptom score, 1.20 versus 0.82). At the long-term follow-up point, the IT group continued to experience an improvement in symptoms (1.2–1.26), while the medically managed controls saw no change in symptoms after 4 months (0.82–0.82). Conclusions from this data are limited because there were no baseline symptom scores to ensure equality at baseline, no statistics for significance, and no specific information on the assessed symptoms identified in this article.

A group of investigators at the University of Texas Southwestern Medical Center also examined symptoms of atopic CRS groups with and without IT intervention, but focused their studies on patients with AFRS and only collected data at fixed points in time in 1998 and 2002 for patients that had at least 12 and 48 months of follow-up, respectively.^{15,16} No baseline data were recorded, but treatment protocols were standardized in a prospective manner. The earlier study reported less severe symptoms on the Chronic Sinusitis Survey in 11 AFRS patients treated with IT for at least 12 months when compared with 11 AFRS patients not receiving IT (71 versus 49; $p = 0.002$).¹⁵ In

the subsequent study, 10 AFRS patients who had been treated with IT at some point during the study period were compared with 7 AFRS non-IT controls using a 20-item Sino-Nasal Outcome Test symptom survey at an average follow-up of 82 months. Symptom scores were comparable between the two groups and averaged higher than the validated normal measure of 0.6 (1.64 ± 0.93 versus 1.76 ± 1.04 ; $p > 0.05$).^{16,19}

The only other study to examine the effects of IT on sinusitis symptoms was a retrospective case series of 114 patients with AR and a diagnosis of recurrent sinusitis with radiographic evidence. Each patient was on IT as part of their treatment regimen for at least 12 months. An adapted form of the Rhinitis Outcomes Questionnaire that included sinusitis-specific symptoms of sinus pain, green/yellow nasal mucus, and nasal blockage was administered twice during a singular office visit, once to recall symptoms before starting IT treatment and once to establish current symptoms. A significant improvement was reported in overall symptom scores (56.4 ± 23 to 28.6 ± 21 ; $p < 0.001$) and decreases of 61, 50, and 49% observed in sinus pain, nasal mucus, and nasal blockage, respectively.¹⁷ Unfortunately, a formal meta-analysis of these studies was not possible because of severe heterogeneity of data and failure of many studies to capture and report baseline symptoms scores.

Endoscopic Exam

Endoscopic measures of disease were reported in four articles.^{12,13,15,16} Turbinate hypertrophy was estimated during the endoscopic exam of atopic children with CRS after 2–3 months with or without IT treatment. Hypertrophy was significantly reduced in the IT treatment group after treatment (1.52 ± 0.51 to 0.37 ± 0.50 ; $p < 0.01$) but unchanged in the control group (1.53 ± 0.74 to 1.40 ± 0.63 ; $p > 0.05$). Hypertrophy was equal between the groups at baseline and was found to be significantly decreased with IT treatment at the study end point (0.37 ± 0.50 versus 1.40 ± 0.63 ; $p < 0.01$).¹²

Middle meatus closure and synechiae formation were established as endoscopic signs of CRS in one study and were reported in postoperative CRSsNP and CRSwNP patients with perennial allergies either receiving IT or other medical management at an average of 14.9 months of follow-up. Middle meatus closure was observed in 5/66 patients using IT and 1/6 atopic controls, and synechiae formation was seen in 8/66 IT patients and 1/6 controls.¹³ The small sample size of the control group limited the usefulness of statistical analysis.

The Kupferberg method of endoscopic staging of AFRS was used in the two cross-sectional studies of IT treatment on AFRS at >12 months and 4 years.^{15,16,20} All patients were assigned a stage of III before endoscopic sinus surgery, and approximately one-half of patients began IT treatment 6–8 weeks postoperatively. At the 1998 follow-up, patients receiving IT ($n = 11$) had significantly lower Kupferberg staging than controls ($n = 11$; 1.08 ± 0.67 versus 2.92 ± 0.29 ; $p < 0.001$).¹⁵ At the next measurement in 2002, there was no statistically significant difference between the 10 patients who had received IT and the 7 controls (1.3 ± 0.95 versus 0.57 ± 0.53 ; $p > 0.05$).¹⁶

Polyp Recurrence and Need for Revision Surgery

Polyp recurrence rates were reported by a singular study at a mean follow-up of 14.9 months for patients with CRSwNPs and perennial allergies who had started IT treatment near the time of undergoing functional endoscopic sinus surgery. These rates were compared with atopic patients who opted not to receive IT. Twelve of the 34 patients (35.3%) receiving IT experienced a recurrence in polyps in 13/58 operative sides (22.4%) when compared with 2 of 5 (40%) non-IT patients in 4/8 sides (50%).¹³ The small sample size of the control group limited the usefulness of statistical analysis.

The need for revision surgery was analyzed in a cross-sectional study,¹⁶ a retrospective case series,¹⁷ and a chart review.¹⁸ Marple *et al.* reported no significant difference in number of sinus surgeries be-

Table 1 Characteristics of included studies

Study	Study Design (LOE)	n (IT/Ctrl)	Mean Follow-up (mo)	Diagnosis	Operative Status	Adjunctive Treatment	Outcomes
Asakura 1990 ¹²	Prospective non-RCT (IIa)	37 (20/17)	2.5	CRS in children (polyp status not stated)	No prior surgical treatment	Intranasal lysozyme chloride preparation irrigations, antihistamines as needed	IT group had less rhinorrhea, discharge, and nasal obstruction, IT group had significantly less turbinate hypertrophy, IT group had smaller maxillary XP shadow (better radiographic outcome)
Nishioka 1994 ¹³	Prospective non-RCT (IIa)	72 (66/6)	14.9	CRSsNP and CRSsNP	Postoperative	INCS	Insufficient evidence to assess polyp recurrence and insufficient evidence to assess endoscopic middle meatus closure and syneciae formation
Schlenter 1983 ¹⁴	Prospective non-RCT (IIa)	31 (15/16)	45.5	CRSsNP and CRSsNP	Postoperative	Systemic steroids, INCS	IT group had less severe symptom scores at 4 mo with continued improvement on long-term follow-up and IT group had greater improvement from baseline radiographic score
Folker 1998 ¹⁵	Cross-sectional study of prospective protocol (IIb)	22 (11/11)	33	AFRS	Postoperative	Systemic steroids, nasal irrigation, and INCS	IT group had less severe symptoms scores on Chronic Sinusitis Survey, lower average Kupferberg endoscopic stage in IT group, and decreased need for INCS and oral steroids in IT group
Marple 2002 ¹⁶	Cross-sectional study of prospective protocol (IIb)	17 (10/7)	82	AFRS	Postoperative	Nasal irrigation, antihistamine, and INCS	IT group with no benefit in SNOT-20 symptom scores, number of revision surgery, endoscopic stage, or oral steroid/antibiotic courses
Nathan 2004 ¹⁷	Retrospective case series (III)	114 (114/0)	39.6	CRSsNP	NS	Antibiotics	IT gives improvement in modified Rhinitis Outcomes Questionnaire score over time with noted decrease in sinus pain, green/yellow mucus, and nasal blockage; and 54% fewer surgeries per year after starting IT
Bassichis 2001 ¹⁸	Retrospective chart review (III)	60 (36/24)	48.5	AFRS	Postoperative	Nasal irrigation, INCS, heated mist, systemic steroids, oral antibiotics, in-office procedures, and revision surgeries	IT group with fewer revision surgeries and IT patients had fewer office visits for sinusitis interventions per year

SNOT-20 = 20-item Sino-Nasal Outcome test; RCT = randomized controlled trial; CRS = chronic rhinosinusitis; CRSsNP = chronic rhinosinusitis with nasal polyps; CRSsNP = chronic rhinosinusitis sans nasal polyps; AFRS = allergic fungal rhinosinusitis; INCS = intranasal corticosteroids; NS = not specified; IT = immunotherapy; ctrl = control; LOE = level of evidence (turur.cebm.com 2009).

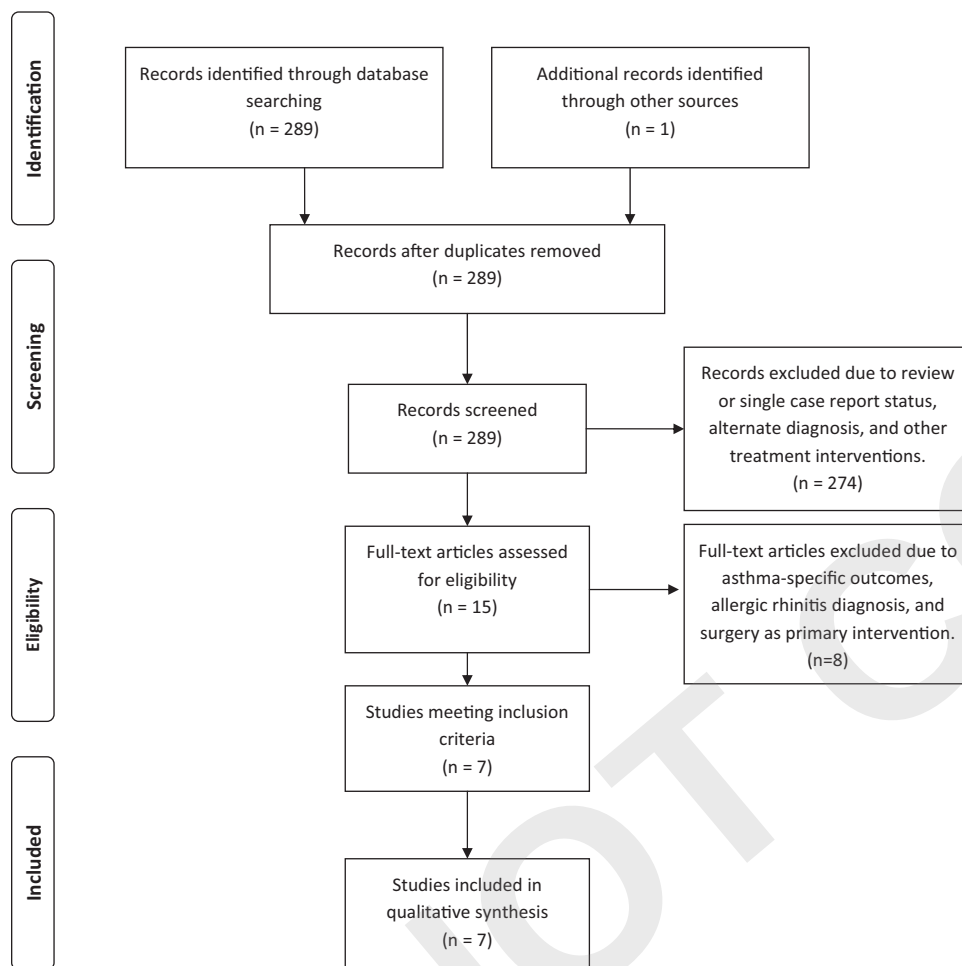


Figure 1. PRISMA flowchart outlining search strategy. (Adapted from Ref. 10.)

tween the IT and non-IT AFRS groups during the average 82-month follow-up period (2 ± 1.33 versus 1.86 ± 0.90 ; $p > 0.05$). Nathan *et al.* determined the quantity of surgical procedures, which included surgeries for the nose, ears, or sinuses, through a recall-based questionnaire and reported a 54% decrease in procedures in the year after the initiation of IT treatment compared with the year before treatment. Raw data and statistical significance were not reported. Finally, Bassichis *et al.* reviewed medical records of 60 postoperative AFRS patients, 36 of which had been treated with IT and had at least 1 year of consistent follow-up. The patients receiving postoperative IT had significantly fewer revision sinus surgeries than those who decided not to use IT (4/36 versus 8/24; $p < 0.01$).

Radiographic Assessment

The sinuses of study patients were examined using radiographic techniques in two of the articles identified.^{12,14} Asakura *et al.* used an unidentified method of radiographic assessment that measured the “XP shadow of maxillary sinus,” with higher values indicating more severe disease. The 20 perennially atopic children undergoing medical management for CRS with adjunctive subcutaneous IT had less severe radiological evidence of disease than the 17 children not receiving IT (0.83 ± 0.87 versus 1.47 ± 0.86 ; $p < 0.01$), although both groups showed substantial improvement from equivalent baseline values ($p < 0.01$). Schlenter *et al.* described a computed tomography and ultrasound-based scoring system for sinusitis with a maximum of 7 points for severe disease featuring mucosal swelling (3 points) and cysts or secretion (2 or 4 points). This radiographic score was established before treatment and at long-term follow-up of 4.13 or 3.47

years for the atopic groups receiving IT ($n = 15$) and standard medical treatment ($n = 16$) respectively. The IT group saw an improvement in the radiographic score of 40% during this time frame ($6.00 \rightarrow 3.59$), whereas the control group improved only 27% ($6.92 \rightarrow 5.06$). No statistics for significance were identified in the review of this article.

Need for Corticosteroids or Antibiotics

Two cross-sectional studies of the same cohort at different time points assessed the need for systemic corticosteroids in AFRS patients using IT versus those using standard medical management alone.^{15,16} After an average 33-month follow-up, no oral steroid was needed in the group receiving IT ($n = 11$), whereas oral steroids were required in every patient on average twice per year in the medically managed control group ($n = 11$; $p < 0.001$).¹⁵ However, after a longer follow-up (average, 82 months), systemic corticosteroids were required by 4 patients in both the IT ($n = 10$) and the control ($n = 7$) groups (average, 1.1 versus 1.29 courses per year; $p > 0.05$).¹⁶

Intranasal steroid use was assessed in the earlier cross-sectional study with a reported 3/11 AFRS patients receiving IT requiring continuous intranasal steroid use compared with 8/11 AFRS medically managed controls ($p = 0.043$).¹⁵ It was also mentioned that the 3 control patients who discontinued intranasal steroids claimed ineffectiveness as the cause.

Oral antibiotic use in AFRS patients with or without IT use was documented in the long-term, 82 month follow-up, with no significant differences observed between the two treatment groups (90% versus 86% of patients; 3.8 ± 4.6 versus 2.5 ± 2.1 courses; $p > 0.05$).¹⁶

Average Number of CRS-Related Office Visits

One retrospective chart review reported the average number of office visits for sinus complaints in patients with AFRS.¹⁸ Overall, there was a significant difference in yearly office visits for sinusitis management between a group of 36 patients who had received IT and a control group ($n = 24$) treated pharmacologically (3.17 versus 4.7; $p < 0.05$). Additionally, in a group of patients that delayed initiation of IT after surgery, the average number of office visits seeking intervention for sinus complaints per patient per year decreased from 5.0 to 2.57 after starting treatment ($n = 7$; $p < 0.01$).

DISCUSSION

This review identified three prospective non-RCTs, two cross-sectional studies of a prospective protocol, a retrospective case series, and a retrospective chart review that report sinus-specific outcomes after IT in patients with CRS. With regard to the primary outcome of interest, four of five studies reported a statistically significant reduction in symptoms in patients receiving adjuvant IT compared with patients on standard medical management alone. Interestingly, the one study that did not find a difference in symptoms had the longest follow-up (mean of 82 months). In this particular study, IT was given for a standard clinical course of 3–5 years and then discontinued, such that patients may have stopped IT up to 7 years before the end point of data collection. There are a number of possible explanations for lack of efficacy in this specific report. A sizable percentage of patients have been shown to undergo resensitization and/or the development of new sensitizations after IT when followed for many years.^{21,22} Some degree of resensitization is likely to also occur in AFRS treated with IT. There may also have been follow-up bias, wherein patients with consistent follow-up represent a sample set with worse symptoms and thus need for continued care. Finally, AFRS represents a specific subset of CRS, often with a chronic inflammation that can be difficult to control; thus, the long-term effects in this disease subgroup may not be generalizable to other forms of atopic CRS.²³

The strength of conclusions that can be reached with regard to IT in the setting of CRS is severely limited by the quality of available studies. Although some studies were prospective, treatment allocation with regard to IT was not randomized, with patients choosing their own treatment arm. In most studies, baseline characteristics were not reported, and in the cases in which they were, the lack of randomization was apparent with inherent differences between the study groups that were not controlled for in the analysis. The lack of blinding in either the patients or the researchers is another significant area of bias introduced into these studies. A recent systematic review with meta-analysis identified 170 individual RCTs evaluating IT for AR most of which are double blind and of high quality.²⁴ The overwhelming strength of the evidence for IT in isolated AR stands in stark contrast to the data reviewed here with regard to comorbid CRS. Considering the prevalence of atopy in CRS, particularly CRSwNP, the performance of high-quality, double-blinded RCTs should continue to be a high priority for researchers interested in CRS outcomes.

One question that remains is the degree to which sinus-specific outcomes can truly be separated from AR-specific outcomes. There is considerable overlap between AR and CRS symptoms. Similar overlap would be expected in staging systems that include nasal mucosal edema. It remains plausible that improvements in symptoms and mucosal staging highlighted in this study are driven mainly by improvements in AR, as opposed to CRS. One study attempted to modify a validated rhinitis questionnaire to further evaluate sinusitis-related symptoms and had some success in showing an improvement in said symptoms after treatment with IT.¹⁷ More studies aimed at consistent measurement of sinusitis-specific outcome measures are needed to truly delineate the impact of IT on this disease.

CONCLUSION

This study found weak evidence supporting IT as a specific treatment to improve symptoms and clinical measures of CRS when used as an adjunct to traditional therapies, primarily in the postoperative period, with available studies having major limitations. IT is a treatment modality that has the potential for long-term modulation of the underlying immune dysfunction that occurs in CRS. Although the observed improvements in sinonasal symptoms might only reflect optimal treatment of AR, the benefits would be appreciable to patients regardless of the etiology. Prospective, randomized, placebo-controlled trials with consistent sinusitis-specific outcome measures are required to provide high levels of evidence regarding the specific benefits of IT in atopic CRS.

REFERENCES

1. Yehouessi-Vignikin B, and Vodouhe SJ. Maxillary sinusitis: 1752 Cases at the ear-nose-throat department of a teaching hospital in Cotonou, Benin. *Eur Ann Otorhinolaryngol Head Neck Dis* pii: S1879–S7296.
2. Kariyawasam HH, and Rotiroti G. Allergic rhinitis, chronic rhinosinusitis and asthma: Unravelling a complex relationship. *Curr Opin Otolaryngol Head Neck Surg* 21:79–86, 2013.
3. Bunyavanich S, Shargorodsky J, and Celedón JC. A meta-analysis of Th2 pathway genetic variants and risk for allergic rhinitis. *Pediatr Allergy Immunol* 22:378–387, 2011.
4. Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: An updated practice parameter. *J Allergy Clin Immunol* 122:S1–S84, 2008.
5. Settipane RA, Borish L, and Peters AT. Chapter 16: Determining the role of allergy in sinonasal disease. *Am J Rhinol Allergy* 27:S56–S58, 2013.
6. Marple BF. Allergic rhinitis and inflammatory airway disease: Interactions within the unified airspace. *Am J Rhinol Allergy* 24:249–254, 2010.
7. Walker SM, Durham SR, Till SJ, et al. Immunotherapy for allergic rhinitis. *Clin Exp Allergy* 41:1177–1200, 2011.
8. Passalacqua G, Garelli V, Sclifò F, and Canonica GW. Sublingual immunotherapy for allergic rhinitis and conjunctivitis. *Immunotherapy* 5:257–264, 2013.
9. Radulovic S, Calderon MA, Wilson D, and Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev* 12:CD002893, 2010.
10. Erekosima N, Suarez-Cuervo C, Ramanathan M, et al. Effectiveness of subcutaneous immunotherapy for allergic rhinoconjunctivitis and asthma: A systematic review. *Laryngoscope* 124:616–627, 2014.
11. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 151:W65–W94, 2009.
12. Asakura K, Kojima T, Shirasaki H, and Kataura A. Evaluation of the effects of antigen specific immunotherapy on chronic sinusitis in children with allergy. *Auris-Narus-Larynx* 17:33–38, 1990.
13. Nishioka GJ, Cook PR, Davis WE, and McKinsey JP. Immunotherapy in patients undergoing functional endoscopic sinus surgery. *Otolaryngol Head Neck Surg* 110:406–412, 1994.
14. Schlenter WW, and Mann WJ. Operative therapy for chronic sinusitis—Results with allergic and non-allergic patients. *Laryng Rhinol Otol* 62:284–288, 1983.
15. Folker RJ, Marple BF, Mabry RL, and Mabry CS. Treatment of allergic fungal sinusitis: A comparison trial of postoperative immunotherapy with specific fungal antigens. *Laryngoscope* 108: 1623–1627, 1998.
16. Marple B, Newcomer M, Schwade N, and Mabry R. Natural history of allergic fungal rhinosinusitis: A 4- to 10-year follow-up. *Otolaryngol Head Neck Surg* 127:361–366, 2002.

17. Nathan RA, Santilli J, Rockwell W, and Glassheim J. Effectiveness of immunotherapy for recurring sinusitis associated with allergic rhinitis as assessed by the Sinusitis Outcomes Questionnaire. *Ann Allergy Asthma Immunol* 92:668–672, 2004.
18. Bassichis BA, Marple BF, Mabry RL, et al. Use of immunotherapy in previously treated patients with allergic fungal sinusitis. *Otolaryngol Head Neck Surg* 125:487–490, 2001.
19. Bhattacharyya N. Contemporary assessment of the disease burden of sinusitis. *Am J Rhinol Allergy* 23:392–395, 2009.
20. Kupferberg SB, Bent JP III, and Kuhn FA. Prognosis for allergic fungal sinusitis. *Otolaryngol Head Neck Surg* 117:35–41, 1997.
21. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 341:468–475, 1999.
22. Eng PA, Borer-Reinhold M, Heijnen IA, and Gnehm HPE. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. *Allergy* 61:198–201, 2005.
23. Doellman MS, Dion GR, Weitzel EK, and Reyes EG. Immunotherapy in allergic fungal sinusitis: The controversy continues. A recent review of literature. *Allergy Rhinol* 4:e32–e35, 2013.
24. Purkey MT, Smith TL, Ferguson BJ, et al. Subcutaneous immunotherapy for allergic rhinitis: An evidence based review of the recent literature with recommendations. *Int Forum Allergy Rhinol* 3:519–531, 2013. □

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